(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 513 832 A1**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **92108286.3**

(51) Int. Cl.[5]: **A61K 47/14**

(22) Date of filing: **15.05.92**

(30) Priority: **17.05.91 US 701944**
12.11.91 US 790939

(43) Date of publication of application:
19.11.92 Bulletin 92/47

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE

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(54) **Use of dibutyl adipate and isopropyl myristate in topical and transdermal products.**

(57) The present invention relates to compositions for enhancing and/or controlling epidermal, dermal and transdermal penetration of topically applied pharmacologically active agents by use of dibutyl adipate, or a mixture of dibutyl adipate and isopropyl myristate.

EP 0 513 832 A1

The invention relates to the enhancement as well as the control of epidermal, dermal and transdermal penetration of various topically applied pharmacologically active agents utilizing dibutyl adipate or a mixture of dibutyl adipate and isopropyl myristate.

Intravenous infusion, intramuscular injection, buccal, oral, rectal routes, and so forth have been generally adopted as methods for administration of a wide variety of therapeutically active agents, such as antihypertensives, β-Blockers, antiarrhythmics, antianginal agents, vasodilators, antiemetics, antibacterial, antifungals, corticosteroids, retinoids, progestins, estrogens, androgens, analgesics and anti-inflammatories. When these therapeutically active agents are administered to humans or warm blooded animals by such routes, they enter the general circulation and produce the desired systemic therapeutic effect. However, it is well-known that the aforementioned methods of administration have certain disadvantages. For example, the buccal and rectal administration often produce discomfort and aggravation to the patient. The intravenous and intramuscular routes are not only painful for the patient, but also must be performed by trained individuals. Oral administration, although generally acceptable by the patient, may have the disadvantages of poor absorption of the therapeutic agent from the gastrointestinal tract or degradation which may be caused by the acidic medium of the stomach, enzymes in gastrointestinal tract, interaction with ingested food or by rapid metabolism by the liver through which the drug must pass before it enters the systemic circulation.

Recognizing these disadvantages, many investigators have used transdermal route to deliver the therapeutically active agent into systemic circulation. Various therapeutic and cosmetic agents are used for the treatment of a number of skin conditions, for example, hydrocortisone for pruritus and erythema in atopic dermatitis, sulconazole nitrate for fungal infection of the skin, tretinoin for photoaging, and 5-fluorouracil for psoriasis and skin cancer. However, the skin of humans and other warm blooded animals provides an excellent barrier to the penetration of exogenous chemical substances. The outermost layer of the skin, the stratum corneum, offers maximum resistance to penetration, whereas the lower layers are relatively permeable. For the proper treatment of skin disorders or skin diseases, it is important that the pharmacologically active agent penetrates the stratum corneum and is made available at appropriate concentrations at the site of action which can be the stratum corneum, the viable epidermis, the epidermis-dermis junction, the dermis itself, or all the aforementioned layers of the skin depending upon the type of disorder or disease condition.

In certain skin conditions such as ichthyosis, callus or plaque psoriasis, the stratum corneum is thicker and thus can provide a significantly greater barrier to penetration of the drug, reducing its efficacy. However, in a few disease conditions, such as psoriasis, the stratum corneum is not intact and hence is more permeable than normal skin. As the disease or condition improves, there will be restructuring of the barrier and therefore, the resistance for the permeation of the therapeutically active ingredient will increase.

To achieve a consistent supply of therapeutic active ingredient at the site of action during the treatment of skin diseases, it has been found that the use of penetration enhancer is essential. Investigators have turned to various enhancing agents, for example, dimethyl sulfoxide, dimethylformamide, methyldecylsulfoxide (U.S. Patent No. 3,527,864), dimethylacetamide (U.S. Patent No. 3,472,931), and N-alkyl-2 pyrrollidone (U.S. Patent No. 3,696,516), for topical as well as systemic delivery of therapeutic active agents. However, the use of the aforementioned penetration enhancers is not without problems. For example the use of dimethylsulfoxide causes a foul taste and body odor, causes burning and erythema on the skin, reduces the relucency of the lens cortex and causes tissue necrosis in animals (Martindale, The Extra Pharmacopoeia, pages 1461-1463, Twenty-Seventh Edition, 1977). Dimethylformamide and dimethylacetamide also cause a sensation of burning and erythema on the skin. As a result, there exists a need for a novel agent to enhance the absorption through the skin of therapeutic agents which is devoid of the disadvantages and drawbacks that to date have characterized many of the prior art enhancing agents.

The present invention discloses such an agent as dibutyl adipate (DBA) and the combination of dibutyl adipate and isopropyl myristate (IPM).

Dibutyl adipate is marketed under the trade name CETIOL B® by Henkel Corporation as a low fat emollient for cosmetic products. It is disclosed as being a solvent for lipid soluble substances and as possessing good spreading properties. It is also recommended for use in cosmetic products such as hair spray, hair fixatives and hand and body day creams.

Harding, Sohail and Busse, Clinical and Experimental Dermatology, Vol. 10, page 13-21, 1985, have used dibutyl adipate in the cream and ointment formulation of clobetasol propionate. However, their aim was to reduce percutaneous absorption of clobetasol propionate by incorporating in the base an oil, such as dibutyl adipate into which steroids would favorably partition and reduce percutaneous absorption.

Isopropyl myristate is known as a penetration enhancer for topical preparations. However, the applicants are unaware of any reference where a synergestic effect was reported in skin penetration enhancement

from the combination of DBA and IPM.

The present invention discloses that emollient solvents such as dibutyl adipate when used in an optimum amount, alone or in combination with isopropyl myristate, can enhance as well as control the epidermal, dermal and transdermal penetration of various topically applied preparations.

Various dermally effective pharmacological agents are known which can provide beneficial effects when applied topically to the skin to treat surface or subsurface diseases or for creating skin conditions which protect the skin from external factors. Other pharmacological agents are also known which can provide beneficial effects when absorbed into the systemic circulation. A composition of such systemically effective pharmacological agents in combination with dibutyl adipate or a mixture of dibutyl adipate and isopropyl myristate can greatly enhance the rate of penetration of agents through the skin and increase the amount absorbed into the systemic circulation. Thus, it is possible to have a systemic effect through topical application of said composition. The topical delivery of systemically effective pharmacologic agents can be of significant advantage in cases where drugs produce gastric problems, are not well absorbed when given orally, or are rapidly metabolized in the liver, e.g. the "first pass" effect. In such cases, the use of topical delivery can give a systemic response at lower dosage than required orally. Topical delivery also avoids the disadvantages present in the intravenous route of administration, which might otherwise be necessary to achieve effective blood levels at reasonable dosage amounts. Such dermatological agents can be made more beneficial by enhancing their penetration through the protective layer of the skin in accord the with present invention.

The present invention relates to the enhancement as well as the control of epidermal, dermal and transdermal penetration of various topically applied preparations. More specifically, the invention relates to composition and methods for enhancing and/or controlling epidermal, dermal and transdermal penetration of topically applied pharmacologically active agents by use of dibutyl adipate, or a combination of dibutyl adipate and isopropyl myristate.

An object of the present invention is to provide a novel agent for enhancing and/or controlling skin permeation of therapeutic agents.

It is also an object of the present invention to provide a novel agent which will enhance and/or control epidermal and dermal absorption of dermatological (that is, cosmetic or therapeutic) agents and enhance and/or control delivery through the skin and into the general circulation of systemically active therapeutic agents.

Another object of the invention is to provide an enhancing agent which is devoid of side effects.

Yet another object of the invention is to provide a novel composition utilizing such novel enhancing agents, which formulations are useful for topical application.

Still another objective of the invention is to provide a method for enhancing the skin penetration of therapeutic chemicals.

Other objectives, features and advantages of the invention will be apparent to those skilled in the art upon a study of this disclosure and appended claims.

Figure 1 shows the skin penetration of halobetasol propionate from FN9-28150-73 cream, FN9-28150-71 cream and Ultravate Ointment.

Figure 2 shows the skin penetration of halobetasol propionate from FN9-28150-79 ointment, FN9-28150-80 ointment and Ultravate Ointment.

Figure 3 shows the skin penetration of BMY 30047 from cream formulations FN9-28190-56, FN9-28190-51, FN9-28190-63 and 30047-C-03-A.

Figure 4 shows the results of rhino mouse assay of FN9-28190-20 in comparison to Retin A.

It has been found that the dermal and transdermal penetration of a pharmacologically active compound can be substantially improved by incorporating the compound into a composition containing a dermal and transdermal effective amount of dibutyl adipate or a mixture of dibutyl adipate and isopropyl myristate.

This unexpected effect is quite useful in that it allows one to improve the dermal and transdermal delivery of pharmacologically active compounds from the composition, thereby allowing one to achieve the same level of efficacy with a lower overall concentration of the pharmacologically active compound in the composition.

The objectives of the present invention can be achieved by employing an effective amount of dibutyl adipate or a mixture of dibutyl adipate and isopropyl myristate, as the enhancing agent, in a composition of matter further comprising at least one therapeutic agent.

The composition of the present invention may also contain other ingredients of the type commonly employed by those skilled in the art of compositions for topical application. These may include, for example, carriers, emollients, surfactants and/or an additional penetration enhancer.

A composition can be any suitable non-toxic or pharmaceutically acceptable topical carrier material or

vehicle such as a solution, suspension, emulsion, lotion, cream, gel, ointment, liposomes, aerosol spray, polymeric gel, sol, a cataplasm, a plaster, a patch, film, or a tape preparation, which are well-known to those skilled in the art of topical pharmaceutical formulation.

The methods of this invention apply to topical compositions containing a wide variety of pharmacologically active agents including but not limited to:

Antihypertensives, such as clonidine, α-methyldopa, captopril, spironolactone; antiangina drugs and vasodilators such as nitroglycerin, isosorbide dinitrate and dipyridamole; β-Blockers such as propranolol, bupranolol, timolol and nadoxolol; sex hormones such as estrogens, androgens, estradiol, testosterone, and progesterone; antiasthma drugs such as cromoglycic acid; antihistamines such as tripelennamine, triprolidine, diphenhydramine and chlorpheniramine; antibiotics such as penicillins, cephalosporins, tetracyclines, polymyxin B, bacitracin and novabiocin; antifungal agents such as sulconazole, nystatin, amphotericin B and griseofulvin; deodorants such as benzalkonium chloride and neomycin sulfate; antiulcer drugs such as cimetidine and ranitidine; antispasmodics such as dicyclomine hydrochloride; and other drugs effecting the gastrointestinal tract such as atropine; NSAIDS (non-steroidal anti-inflammatory agents) such as aspirin, ibuprofen, phenylbutazone, and indomethacin; analgesics such as aspirin and ibuprofen; antipyretics such as aspirin, ibuprofen, acetaminophen and phenacetin; steroids such as hydrocortisone, prednisolone, betamethasone and triamcinolone; sympathomimetic amines such as xylometazoline, phenylephrine and naphazoline; central nervous system active agents such as amphetamine, phenylpropanolamine and butorphanol; diuretics such chlorothiazide, hydrochlorothiazide and benzthiazide; antitussives such as codeine, dextromethorphan and diphenhydramine; vasodilators such as hydralazine, enalapril maleate nitroglycerin; antiemetics such as chlorpromazine, meclizine; compounds for treating motion sickness such as promethazine, dimenhydrinate meclizine; antipsoriasis compounds such as anthralin, MC 903, tretinoin; hair growth promoters such as minoxidil; drugs affecting the skin; antiphoto-aging compounds such as retinoids, arotinoids; protein and peptide drugs such as insulin, TGFα and TGFβ, antiviral drugs such as acyclovir; drugs to treat ichthyosis such as ammonium lactate; and drugs to treat disturbed keratinzation of skin such as α or β hydroxycarboxylic acid and related ketocarboxylic acid and ester, lactones or salt forms thereof.

Preferably the pharmacological agent is from about 0.001% wt to about 80% wt of total composition. However, the effective amount of a specific pharmacological agent will vary in accordance with parameters well understood by the physician or veterinarian. These parameters include the condition being treated, the age, weight and physical condition of the subject, and of course, the specific agent selected.

The optimum level of DBA or a mixture of DBA and IPM may be readily evaluated by a few simple tests such as those described herein.

In general, for a given label strength of a pharmacologically active agent, it is preferred to use a minimum amount of solvent DBA, or DBA and IPM to dissolve the drug completely and yet maintain favorable partition coefficient and diffusion through the stratum corneum of the skin.

The general rate of penetration is in order of optimal solubilized solution > dilute solution. It is also necessary to consider the contribution of other solvents on the solubility of the given strength of the pharmacologically active agent in the composition. Generally, the concentration of DBA is about 0.1% wt % to about 99 wt % and the concentration for IPM is from 0 wt % to 99.9 wt %. The more preferred concentration of DBA is from about 0.1 wt % to about 50 wt % and of IPM is from about 1 wt % to about 30 wt %. All percentages of composition components recited are, unless otherwise indicated, weight percentage (wt %) and are based upon the weight of the composition.

The present invention will be described with reference to the examples below but it is not deemed to be limited only to these examples.

EXAMPLE 1

In Vitro Skin Penetration Study

The following test method may be employed with human skin to determine epidermal or dermal or transdermal penetration of pharmacologically active compounds used in the practice of this invention. The procedure is also applicable to skin of other warm blooded animals.

Skin Preparation

Normal excised human skin obtained from breast reduction or abdominal skin samples obtained from the Firefighters Skin Bank were used. The skin samples were stored in a freezer at -30°C until needed.

Only skin that appeared normal was used. Historical evidence of chronic illness, skin disease or skin injury excluded use of skin samples in the study.

The skin obtained from the Firefighters Skin Bank was supplied as sterile, split-thickness skin with most of the underlying dermis already removed. The skin was thawed and rinsed in normal saline for about 30 minutes prior to use.

The skin obtained from breast reduction autopsy was full thickness skin. It was thawed at room temperature in normal saline followed by freezing on a microtome with carbon dioxide and sectioning to a layer around 200 micrometers thick. It was then stored in normal saline at 5°C until about 8 hours before use.

Skin Penetration

The skin sections were mounted on flat-top Franz diffusion cells with a diffusional cross-section of 0.636 cm^2 or 1.8 cm^2. A 50 or 100 microliter sample of test formulation was placed on the stratum corneum surface of the skin in the donor compartment and the receptor compartment was filled with 4 to 8 ml of normal saline or 30% isopropanol in water. The selection of receptor fluid depended on the drug candidate whose penetration had to be evaluated. The main objective was to maintain sink conditions in the receptor compartment. The receptor fluid was well stirred throughout the experiment and the temperature was maintained by circulating water at 37°C through the water jacket of the diffusion cell. A 150 to 500 microliter sample was withdrawn from the receptor compartment at appropriate intervals and analyzed for drug content by HPLC or by scintillation counter for radioactive drug. The receptor fluid was replenished with normal saline after each withdrawal. All the receptor fluid and replenished fluid was thoroughly degassed before use.

EXAMPLE 2

Halobetasol propionate (BMY 30056) is an ultra-potent steroid used topically for the treatment of dermatological conditions such as eczema and psoriasis. Halobetasol propionate is commercially available by Bristol-Myers Squibb as ULTRAVATE Cream and ULTRAVATE Ointment. The composition of these commercial products and also several experimental formulations are given in Table 1 and Table 2. ULTRAVATE Cream is an oil in water emulsion containing isopropyl palmitate and isopropyl isostearate as emollients. The ULTRAVATE Ointment is a nonaqueous emulsion of propylene glycol in a petrolatum base. The in vitro human skin penetration of these two compositions and experimental formulation FN8-1089-25 cream is given in Table 3 under Study I. It is observed that the ULTRAVATE Cream has lower skin penetration than ULTRAVATE Ointment. The presence of the emollients isopropyl palmitate and isopropyl isostearate, which are known to have a similar penetration enhancement property to isopropyl myristate, did not enhance the penetration of halobetasol propionate from ULTRAVATE Cream in comparison to ULTRAVATE Ointment. The increase in skin penetration of halobetasol propionate from ULTRAVATE Ointment can be due to the presence of the penetration enhancer propylene glycol, as well as due to occlusion provided by petrolatum. The experimental cream FN8-1089-25 having 15 wt % dibutyl adipate (DBA) and 7 wt % propylene glycol (PG) showed poor penetration in comparison to ULTRAVATE Ointment and was not superior to ULTRAVATE Cream. The poor penetration of this experimental formulation is due to oversolubilisation of halobetasol propionate in the cream vehicle by dibutyl adipate and the resulting reduction of partitioning of halobetasol into the skin. These findings are similar to those reported by Harding et al. (Clinical and Experimental Dermatology, Vol. 10, page 13-21, 1985) who, when using 18 wt % DBA and 10 wt % PG in clobetasol propionate cream formulation, observed reduced penetration of clobetasol propionate. These findings confirm that DBA reduces percutaneous absorption of therapeutic agent when used in a concentration which oversolubilizes the drug in the formulation.

In a different human skin study, the in vitro skin penetration of halobetasol propionate from ULTRAVATE Ointment, FN8-1114-16 cream and FN8-1114-13 cream were evaluated (Table 3, Study II). ULTRAVATE Ointment was used as a control in order to normalize the data, and to assist in the comparison of skin penetration of different formulations when evaluated for skin penetration in different human skin. The rank order of penetration at 72 hours is ULTRAVATE Ointment > FN8-1114-16 cream > FN8-1114-13 cream.

ULTRAVATE Cream contains isopropyl palmitate and isopropyl isostearate, which are reported to have skin penetration enhancement properties similar to isopropyl myristate (IPM). However, ULTRAVATE® Cream containing these fatty acid esters shows poor penetration in comparison to Ultravate Ointment (Table 3, Study I). The cream formulation FN8-1114-16 containing 6 wt % IPM and 2 wt % DBA shows about a five-fold increase in skin penetration than ULTRAVATE Cream (compare results from Study I and Study II,

Table 3) and has about four-fifths of the penetration of ULTRAVATE Ointment.

Cream formulation FN8-1114-13 containing 6 wt % IPM + 2 wt % DBA + 23 wt % PG showed about 3 times more penetration than ULTRAVATE Cream but was not superior to ULTRAVATE Ointment nor the cream FN8-114-16.

It can be concluded from Study I and Study II that (a) by using an optimum amounts of DBA and IPM which are just sufficient to dissolve halobetasol propionate in the cream, one can enhance the skin penetration of halobetasol propionate, (b) inclusion of PG, a known penetration enhancer, in the formulation containing optimum amounts of DBA and IPM does not improve the skin penetration of halobetasol propionate any further, and (c)a mixture of DBA and IPM in the new cream formulation showed better skin penetration of halobetasol propionate than Ultravate Cream having a mixture of isopropyl isostearate and isopropyl palmitate. Hence, the combination of DBA and IPM has a superior skin penetration enhancing property than isopropyl isostearate or isopropyl palmitate or IPM.

The in vitro skin penetration of ULTRAVATE Ointment® (control) and experimental cream FN9-28150-71 and FN9-28150-73 was evaluated in another experiment (Study III, Table 3, Fig. 1). The rank order of penetration at 72 hours is FN9-28150-71 cream ≥ ULTRAVATE Ointment ≥ FN9-28150-73 cream.

The FN9-28150-71 cream contains 0.5 wt % DBA and 10 wt % IPM as solvents. This solvent mixture results in a saturated solution of 0.05 wt % of halobetasol propionate in the cream formulation. This cream showed about 7.5 times more enhanced skin penetration than ULTRAVATE Cream and was slightly better than ULTRAVATE Ointment (Compare Study III with Study I in Table 3).

The FN9-28150-73 cream contains a 4 wt % DBA and 10 wt % IPM as solvents. The solvent concentration in this formulation is slightly in excess of what is necessary to dissolve the given strength of halobetasol propionate in the formula. Therefore, it gave comparatively less skin penetration than that of the formula having a saturated solution eg. FN9-28150-71 cream.

Generally petrolatum-based ointments, because of their occlusive nature, show superior skin penetration of pharmacologically active agents as compared to that of cream formulations. The present invention demonstrates that one can formulate cream formulations having appropriate proportions of IPM and DBA, to obtain skin penetration similar to or better than that of ointments.

Petrolatum-based ointments are also greasy in nature and in certain instances it may be desired to have cosmetically elegant (less greasy) topical products, such as creams, lotions, gels and solutions having penetrations of the pharmacologic active similar to that of an ointment. The present invention demonstrates such an achievement and therefore, the more cosmetically elegant formulation.

It is also clear from the above examples (Figure 1) that it is possible to control the rate of penetration of drug by just changing the proportion of DBA and IPM in the formula (compare example FN9-28150-71 with FN9-28150-73). This concept is very useful in dermal and transdermal products to control the rate of delivery of the drug to the site of action.

The in vitro skin penetration data of halobetasol propionate ointments FN9-28150-79 and FN9-28150-80, and commercial ULTRAVATE Ointment as a control is shown in Fig. 2, and Study IV of Table 3. The rank order of penetration is FN9-28150-80 ointment > ULTRAVATE Ointment ≥ FN9-28150-79 ointment.

The FN9-28150-79 ointment contains 2 wt % DBA and 6 wt % IPM in an optimum amount, just enough to dissolve halobetasol propionate in the ointment formulation. This new ointment gave penetration similar to that of the ULTRAVATE Ointment containing PG as an enhancer.

The FN9-28150-80 ointment is similar to the FN9-28150-79 ointment but it contains ozokerite. This new ointment showed 1.5 times more penetration than ULTRAVATE Ointment or the FN9-28150-79 ointment. This improved penetration is due to the use of an optimum mixture of IPM and DBA and may be due to the enhanced occlusion obtained by incorporating ozkerite in the ointment base.

It is a common practice to use PC as a penetration enhancer in dermal and transdermal preparations. PG, as discussed earlier, can be a sensitizer and irritant when applied topically. The side effects of PG are more pronounced in an occluded condition such as occurs in the application of an ointment or a transdermal patch (C. Huriez, P. Martin and M. Mennecier, L'allergie au propylene glycol, Rev. Franc. Allerg., Vol. 6: pages 200-205, 1966; M. Hannuksela, V. Pirila and O.P. Salo, Skin reactions to propylene glycol, Contact Dermatitis, Vol. 1: pages 112-116, 1975; S. Agren-Jonsson and B. Magnusson, Sensitization to propantheline bromide, trichlorocarbanilide and propylene glycol in an antiperspirant, Contact Dermatitis, Vol. 2: pages 79-80, 1976; and K. Motoyoshi, S. Nozawa, M. Yosimura and K. Matsada, The safety of propylene glycol and other humectants, Cosmet. Toilet., Vol. 99: pages 83-91, October 1984.) The present invention demonstrates that by incorporating optimal amounts of dibutyl adipate and isopropyl myristate into a topical formulation, the formulation can have the benefits of enhanced skin penetration of pharmacologically active compounds without the use of propylene glycol or the possible associated irritation or sensitization.

Table 1

Composition of 0.05 wt % halobetasol propionate commercial cream (ULTRAVATE®) and experimental cream formulations.

Ingredient	ULTRAVATE Cream® % w/w	FN8-1089-25 % w/w	FN8-1114-16 % w/w	FN8-1114-13 % w/w	FN9-28150-71 % w/w	FN9-28150-73 % w/w	Rationale
Halobetasol Propionate	0.05	0.05	0.05	0.05	0.05	0.05	Active Ingredient
Dibutyl Adipate	—	15.00	2.00	2.00	0.50	4.00	Solvent/emollient
Isopropyl Myristate	—	—	6.00	6.00	10.00	10.00	Solvent/emollient
Isopropyl Isostearate	3.00	—	—	—	—	—	Solvent/emollient
Isopropyl Palmitate	2.00	—	—	—	—	—	Solvent/emollient
Propylene Glycol	—	7.00	—	23.00	—	—	Solvent
Steareth-21	3.00	2.50	—	2.50	—	—	Emulsifying agent
Laureth-23	—	—	0.50	—	0.50	0.50	Emulsifying agent
Steareth-2	—	2.50	2.50	2.50	2.50	2.50	Emulsifying agent
Stearyl Alcohol	—	3.00	—	3.00	—	—	Thickening agent
Cetyl Alcohol	6.00	4.00	1.60	4.00	1.60	1.60	Thickening agent
Dimethicone 200	—	1.00	1.00	—	1.00	1.00	Emollient
Petrolatum	—	—	10.00	6.00	15.00	15.00	Occlusive vehicle
Glycerin	2.0	—	4.00	—	4.00	4.00	Humectant
Trisodium Citrate	—	0.14	—	0.14	—	—	Buffering agent
Citric Acid	—	0.07	—	0.07	—	—	Buffering agent
Carbomer 934®	—	—	0.25	—	0.25	0.25	Thickening agent
Veegum K®	—	—	0.30	—	0.30	0.30	Thickening agent
Kathon CG®	0.05	0.05	0.05	0.05	0.05	0.05	Micropreservative
Germall II	0.2	0.2	0.10	0.10	0.10	0.10	Micropreservative
Na_2EDTA	—	—	0.05	—	0.05	0.05	Chelating agent
Sodium Hydroxide	—	—	0.07	—	0.07	0.07	pH adjustment
Water for production	83.75	64.49	71.60	50.54	64.03	60.53	Vehicle

Table 2

Composition of 0.05 wt % halobetasol propionate commercial ointment (ULTRAVATE®) and experimental ointment formulations.

Ingredients	ULTRAVATE Ointment % w/w	FN9-28150-79 % w/w	FN9-28150-80 % w/w	Rationale
Halobetasol Propionate	0.05	0.05	0.05	Active Ingredient
Dibutyl Adipate	---	2.00	2.00	Solvent/emollient
Isopropyl Myristate	---	6.00	6.00	Solvent/emollient
Propylene Glycol	7.50	---	---	Solvent
Dehymuls E®	7.50	7.50	7.50	Emulsifying agent
Bees Wax	5.00	7.50	2.50	Thickening agent
Ozokerite	---	---	5.00	Occlusive vehicle
Petrolatum	79.95	76.95	76.95	Occlusive vehicle

Table 3
In-vitro skin penetration of 0.05 wt % halobetasol propionate from different formulations.

Formulation	Amount penetrated in 72 hours (micrograms)*	Amount penetrated in percentage relative to ULTRAVATE Ointment as Control
Study I		
ULTRAVATE® Ointment (PG 7 wt %)	2.29	100.00
ULTRAVATE® Cream (Isopropyl isostearate 3 wt % + Isopropyl palmitate 2 wt %)	0.38	16.59
FN8-1089-25 cream (DBA 15 wt % + PG 7 wt %)	0.35	15.28
Study II		
ULTRAVATE® Ointment (PG 7 wt %)	4.76	100.00
FN8-1114-16 cream (DBA 2 wt % + IPM 6 wt %)	3.9	81.90
FN8-1114-13 cream (DBA 2 wt % + IPM 6 wt % + PG 23 wt %)	2.15	45.16
Study III		
ULTRAVATE® Ointment (PG 7 wt %)	3.75	100.00
FN9-28150-71 cream (DBA 0.5 wt % + IPM 10 wt %)	4.75	126.00
FN9-28150-73 cream (DBA 4 wt % + IPM 10 wt %)	2.61	69.6
Study IV		
ULTRAVATE® Ointment (PG 7 wt %)	3.75	100.00
FN9-28150-79 ointment (DBA 2 wt % + IPM 6 wt %)	3.48	92.80
FN9-28150-80 ointment (DBA 2 wt % + IPM 6 wt % + Ozokerite 5 wt %)	5.57	148.50

* Amount in micrograms penetrated per cm^2 area of the skin. The results are average of multiple determinations.

EXAMPLE 3

Rhino Mouse Utricle Model To Evaluate Efficacy Of Retinoid Formulations

The skin of rhino mouse is characterized by the presence of numerous large cysts resembling comedones (S. J. Mann, Hairloss and cyst formation in hairless and rhino mutant mice, Anat. Rec., Vol. 170, pages 485-500, 1971) and is useful as a model system for the pharmacologic testing of agents, such as retinoids, for the treatment of acne (R. E. Ashton, M. J. Connor and N. J. Lowe, Histological changes in the

skin of the rhino mouse induced by retinoids, J. Invest. Derm., Vol. 82: pages 632-635, 1984; E. J. Van Scott, Experimental animal integumental models for screening potential dermatologic drugs, in: Advances in Biology of the Skin, Vol. XII, Pharmacology and the Skin, W. Motagna, E. J. Van Scott and R. B. Stoughton, Editors, Meredith Corporation, New York, pages 523-531, 1972.) The experimental details of the model used to evaluate the efficacy of tretinoin formulations are given below.

Female rhino mice were obtained from the Skin and Cancer Hospital, Temple University, Philadelphia, Pennsylvania. Upon receipt, the rhino mice were treated with an anti-parasitic agent, trichlorfon (COMBOT®), to rid them of pinworms. It was administered in their drinking water for two weeks. An additional two weeks was allowed to pass without COMBOT treatment before mice were placed on study. Animals were housed in accordance with the National Institute of Health guidelines and had free access to food and water. At the time of the study initiation, the mice were 9-14 weeks old.

The mice were individually housed in a plastic shoe box cage with corn cob bedding and placed in rooms lighted with yellow lights, cycled for 12 hours on and 12 hours off during the study.

The mice were divided into groups of five and their contralateral flank sites were treated with 50 microliters test formulations and vehicle or ethanol. One group of mice was run as a control with treatment of vehicle or ethanol. Animals were treated once a day for five days.

Two days after the last treatment, the animals were sacrificed by CO_2 inhalation, and the skin sections from the test and control sites were taken. Excessive fat and connective tissue from the subcutaneous region of the skin were removed using a scalpel. The skin was then placed on filter paper and a biopsy of 7/8" of the circular area of skin was removed by arch punch. The epidermal sheet from the biopsy was separated from the dermis after incubation in 0.5% acetic acid solution for 10-20 hours at 4°C. These sheets were then fixed in formalin, dehydrated with ethanol and cleared in xylene.

The sheets were then evaluated for changes in the sizes of the utriculi as follows: The maximum diameter of 20 representative utriculi per tissue sample were measured, using an IBM PC computer image measurement program (Microscience, Inc., Federal Way, Washington D.C.) and an Olympus microscope (200x magnification).

Retinoid effects were evaluated as a percent reduction in utricle diameter by comparing mean diameter of the vehicle treated groups to that of formulation treated groups.

EXAMPLE 4

Formulations containing 1% BMY 30047 (11-cis, 13-cis-12-hydroxymethyl retinoic acid, delta lactone) developed in a vehicle (30047-C-03-A) similar to the marketed RETIN-A cream and in other experimental creams are shown in Table 4 and Table 5 respectively.

The in vitro human skin penetration of BMY 30047 from these formulations is shown in Fig. 3 and Table 6. The rank order of penetration is FN9-28140-56 cream ≥ FN9-28150-51 cream ≥, FN9-28150-63 cream ≥, 30047-C-03-A cream.

The FN9-28190-56 cream containing 20 wt % DBA and 10 wt % IPM gave as much as nine times the skin penetration of BMY 30047 than that of the cream having 15 wt % IPM and 0.1 wt % sodium lauryl sulfate (30047-C-03-A) and the cream containing 10 wt % IPM, 20 wt % Capmul MCM and 0.1 wt % octoxynol-9 (FN9-28190-63).

The skin penetration of the cream containing 30 wt % DBA (FN9-28150-51) was about one-half the penetration of the cream containing 20 wt % DBA and 10 wt % IPM (FN9-28190-56) and about five times the penetration of the other two experimental creams.

It can be concluded from this study that dibutyl adipate enhances the skin penetration of BMY 30047 and that the skin penetration is further enhanced when isopropyl myristate is used in conjunction with dibutyl adipate. The data suggests that there is synergism in penetration enhancement when DBA and IPM are used together.

Table 4

Composition 1 wt % BMY 30047 Cream (30047-C-03-A)		
Ingredient	30047-C-03-A % w/w	Rationale
BMY 30047	1.00.	Active Ingredient
Stearic Acid	18.00	Thickening Agent
Isopropyl Myristate	15.00	Solvent/Emollient
PEG-40-Stearate	5.00	Emulsifying Agent
Stearyl Alcohol	2.00	Thickening Agent
Xanthan Gum	0.60	Thickening Agent
Sorbic Acid	0.20	Micropreservative
BHA	0.10	Antioxidant
BHT	0.10	Antioxidant
Sodium Lauryl Sulfate	0.10	Emulsifying Agent
Water for Production	57.90	Vehicle

Table 5

Composition of 1 wt % BMY 30047 creams				
Ingredient	FN9-28190-56	FN9-28190-51	FN9-28190-63	Rationale
BMY 30047	1.00	1.00	1.00	Active Ingredient
Dibutyl Adipate	20.00	30.00	---	Solvent/Emollient
Isopropyl Myristate	10.00	---	10.00	Solvent/Emollient
Capmul MCM®	---	---	20.00	Solvent/Emollient
Octoxynol-9	---	---	0.10	Emulsifying Agent
Steareth-2	2.50	2.50	2.50	Emulsifying Agent
Steareth-21	2.50	2.50	2.50	Emulsifying Agent
Cetyl Alcohol	2.00	2.00	2.00	Thickening Agent
BHA	0.075	0.075	0.075	Antioxidant
BHT	0.075	0.075	0.075	Antioxidant
Stearyl Alcohol	7.00	7.00	7.00	Thickening Agent
Glyceryl Stearate	1.00	1.00	1.00	Emulsifying Agent
Laureth-4	1.00	1.00	1.00	Emulsifying Agent
Glycerin	2.00	2.00	2.00	Humectant
Na_2EDTA	0.05	0.05	0.05	Chelating Agent
Methyl Paraben	0.20	0.20	0.20	Micropreservative
Propyl Paraben	0.20	0.20	0.20	Micropreservative
Germall II®	0.20	0.20	0.20	Micropreservative
Water for Production	50.20	50.20	50.20	Vehicle

Table 6

In-vitro skin penetration of 1.0 wt % BMY 30047 in different cream formulations.	
Formulation	Amount of BMY 30047 penetrated in 168 hours (micrograms/cm^2)**
FN9-28190-56 (20 wt % DBA + 10 wt % IPM)	45.66
FN9-28190-51 (30 wt % DBA)	23.15
FN9-28190-63 (CAPMUL MCM* 20 wt % + IPM 10 wt % + Octoxynol-9 0.1 wt %)	5.33
30047-C-03-A (IPM 15 wt % + 0.1 wt % SLS)***	4.20

* Capmul MCM is glyceryl caprylate/caprate
** Average of 2 or 3 determinations
*** SLS is sodium lauryl sulfate

EXAMPLE 5

Tretinoin is a retinoid used topically for the treatment of acne, and more recently, A.M. Kligman (U.S. Patent 4,603,146), discloses the use of tretinoin in the treatment of photodamaged human facial skin. Tretinoin is marketed by Johnson & Johnson under the trade name RETIN-A®.

The composition of the experimental 0.01 wt % tretinoin cream formulation is given in Table 7. For the purpose of evaluating the efficacy of tretinoin in experimental formulation in comparison to the marketed RETIN-A cream they were evaluated in the rhino mouse utricle model. The test results are shown in Figure 4. The rank order of efficacy is: RETIN-A cream (0.1 wt %) > FN9-28190-20 cream (0.01 wt %) = RETIN-A cream (0.05 wt %) > RETIN-A cream 0.025 wt %.

The FN9-28190-20 cream contains 3 wt % DBA, in an amount just sufficient to solubilize the tretinoin in the formulation. It is clear from this example that the formulation containing DBA increases the efficacy and hence the topical bioavailability of tretinoin. The FNO-28190-20 cream contains a five-fold reduced amount of tretinoin in comparison to RETIN-A cream containing 0.05 wt % tretinoin while maintaining the same activity.

Table 7

The composition of 0.01 wt % tretinoin cream		
Ingredients	FN9-28190-20 % w/w	Rationale
Tretinoin	0.01	Active Ingredient
Dibutyl adipate	3.00	Solvent/Emollient
Mineral oil	4.00	Solvent/Emollient
Stearyl alcohol	5.00	Thickening Agent
Cetyl alcohol	3.00	Thickening Agent
Steareth-2	2.00	Emulsifying Agent
Steareth 21	2.00	Emulsifying Agnet
Glyceryl Stearate	1.00	Emulsifying Agent
Laureth-4	1.00	Emulsifying Agent
BHA	0.05	Antioxidant
BHT	0.05	Antioxidant
Glycerin	4.00	Humectant
Citric acid	0.004	Chelating Agent
Kathon CG®	0.05	Micropreservative
Germall II®	0.10	Micropreservative
Water purified	74.73	Vehicle

EXAMPLE 6

Ammonium lactate is the ammonium salt of α-hydroxy acid (lactic acid). It is marketed by Westwood-Squibb under the trade name Lac-Hydrin™ for the topical treatment of xerosis and ichthyosis. R. J. Yu et al, (U.S. Patent 4,105,783) and E. J. VanScott et al, (U.S. Patent 4,234,599) disclose the use of α- or β-hydroxy acid or α-keto acids and esters thereof, their amides and ammonium salts for therapeutic treatment of dry skin and skin keratoses.

The composition of experimental creams containing ammonium lactate equivalent to 30 wt % of lactic acid is given in Table 8. Three days prior to the in vitro skin penetration studies the experimental creams were homogeneously mixed with ^{14}C-lactic acid (sodium salt) to result in experimental cream having radioactivity of about 0.01 microCi per mg.

The in vitro human skin penetration data of lactic acid from these formulations is shown in Table 9. The rank order of penetration is FN1-28393-46 > FN1-28393-45 > FN1-28393-47.

The FN1-28393-45 cream contains 5 wt % DBA. This cream showed about 1.4 times more penetration than FN1-28393-47 cream containing 5 wt % mineral oil.

The FN1-28393-46 cream contains 3 wt % DBA and 3 wt % IPM. This showed about 2.2 times more penetration than FN1-28393-47 cream containing 5% mineral oil.

It can be concluded from this study that dibutyl adipate enhances the skin penetration of lactic acid and that the skin penetration is further enhanced when isopropyl myristate is used in conjunction with dibutyl adipate.

Table 8
Composition of experimental creams containing ammonium lactate equivalent to 30 wt % of lactic acid.

Ingredients	FN1-28393-47 % w/w	FN1-28393-45 % w/w	FN1-28393-46 % w/w	Rationale
Ammonium lactate	53.00	53.00	53.00	Active ingredient
Glyceryl stearate and PEG-100 stearate	0.5	0.5	0.5	Emulsifying agent
Mineral oil	5.0	---	---	Emollient
Dibutyl adipate	---	5.0	3.0	Emollient
Isopropyl myristate	---	---	3.0	Emollient
Dimethicone 200	1.0	1.0	1.0	Emollient
Steareth-2	2.5	2.5	2.5	Emulsifying agent
Steareth-21	2.5	2.5	2.5	Emulsifying agent
Stearyl alcohol	3.5	3.5	3.5	Thickening agent
Laureth-4	1.0	1.0	1.0	Emulsifying agent
Cetyl alcohol	0.5	0.5	0.5	Thickening agent
Magnesium aluminum silicate	2.0	2.0	2.0	Thickening agent
Kathon CG®	0.05	0.05	0.05	Micropreservative
Germall II®	0.2	0.2	0.2	Micropreservative
Propylene glycol	5.0	5.0	5.0	Humectant
Water	23.25	23.25	22.25	Vehicle

Table 9

In-vitro human skin penetration of different cream formulations containing ammonium lactate equivalent to 30 wt % of lactic acid.		
Formulation	Amount of C^{14} lactic acid penetrated in 72 hours (DPM/CM^2)*	Amount penetrated in percentage relative to the formulation with mineral oil as a control
FN1-28393-47 (Mineral oil 5 wt %)	13004	100.00
FN1-28393-45 (DBA 5 wt %)	18115	139.30
FN1-28393-46 DBA 3 wt % + IPM 3 wt %)	28817	221.60

*The results are an average of multiple determination

EXAMPLE 7

Twenty - One Day Cumulative Irritation Tests In Humans

This test was conducted to evaluate the irritation and allergic potential of formulations having DBA and IPM combination. This study method and modifications of it have been described in variety of publications. (A. M. Kligman and W. M. Wooding, A method for the measurement and evaluation of irritants on human skin, J. Invest. Dermatol., Vol. 49: pages 78-94, 1967; F. N. Marazulli and H. I. Maibach, in Dermatotoxicology, Ed. 2, Hemisphere Publishing Corporation, pages 167-296, 1983.)

The composition of test formulations BMY 30047 1 wt % cream (30047-C-09-A) and its vehicle 30047-C-10-A cream are given in Table 10. Both test formulations contain 20 wt % DBA and 10 wt % IPM. These test formulations and two control formulations (0.5 wt % sodium lauryl sulfate and RETIN-A® 0.1 wt % cream) were applied to 27 subjects under an occlusive patch for 21 consecutive days. Formulations were re-applied daily, with the exception that patches applied on Saturday were left undisturbed until Monday; the Monday evaluation also recorded for the previous Sunday. Skin reactions were scored on a 5-point grading scale as follows: 0 = no sign of irritation; 1 = slight erythema; 2 = noticeable erythema with slight infiltration; 3 = erythema with marked edema; 4 = erythema with edema and blistering. Once a score of 4 was observed at any site, no further applications were made, and a score of 4 was assigned for the duration of the study. Results were reported by summing scores from all subjects and all visits. Relative irritation potential was estimated based on comparison with scores of the control compounds.

The cumulative irritation potentials of the test formulations and the controls are given in Table 11. Both the test formulations having DBA and IPM were classified as causing "no significant irritation" as they had very low cumulative irritation score; whereas the control products RETIN-A® 0.1 wt % cream and 0.5 wt % sodium lauryl sulfate had a cumulative score of 432.4 and 285.6 respectively and were classified as "moderately irritating".

This study clearly demonstrates that this invention provides us with skin penetration enhancing agents with negligible side effects.

Table 10

Composition of BMY 30047 cream and its vehicle		
Ingredients	30047-C-09-A % w/w	30047-C-10-A % w/w
BMY 30047	1.0	----
Dibutyl Adipate	20.0	20.0
Isopropyl Myristate	10.0	10.0
Steareth-2	2.5	2.5
Steareth-21	2.5	2.5
Stearyl Alcohol	7.0	7.0
Cetyl Alcohol	2.0	2.0
Glyceryl Stearate	1.0	1.0
Laureth-4	1.0	1.0
BHA	0.075	0.075
BHT	0.075	0.075
Glycerin	2.0	2.00
Kathon CG®	0.05	0.05
Germall II®	0.20	0.2
Water for production	50.60	51.60

Table 11

Results of 21-day cumulative irritation test in humans.	
Formulation	Cumulative Irritation Score
30047-C-09-A cream (1 wt % BMY 30047 + 20 wt % DBA + 10 wt % IPM)	30.9
30047-C-10-A cream vehicle (20 wt % DBA + 10 wt % IPM)	24.8
Retin A® 0.1 wt % cream	432.4
0.5 wt % sodium lauryl sulfate in petrolatum	285.6

Claims

1. A topical composition for controlled and enhanced dermal penetration comprising:
   (a) an effective amount of pharmacologically active agent,
   (b) an effective amount of dibutyl adipate or a mixture of dibutyl adipate and isopropyl myristate, or pharmaceutically acceptable acid addition salts thereof, and
   (c) a pharmaceutically acceptable non-toxic topical vehicle.

2. The composition according to claim 1 wherein the pharmacologically active agent is selected from the group consisting of drugs affecting the central nervous system, drugs affecting the cardiovascular system, drugs affecting the gastrointestinal tract, drugs affecting the skin, antifungal agents, antiviral agents, antibiotic agents, antiulcer agents, antispasmodic agents, non-steroidal antiinflammatory agents, analgesics, antihistamine agents, antipyretic agents, antihypertensive agents, vasodilators, antitussives, antiemetic agents, anticancer agents, antipsoriasis agents, antiphoto-aging agents, antiacne agents, antidandruff agents, antikeratoses agents, antiseborrhea agents, antidryskin agents, antidermatitis agents, antiichthyosis agents, carotinoids,retinoids, steroids, sex hormones, vitamins, diuretics, sympathomimetic amines, skin depigmenting agents, skin pigmenting agents, wound healing agents, deodorants, skin moisturizers and hair growth promoters.

3. The composition according to claim 1 wherein the topical composition contains from about 0.1 wt% to about 99 wt% of dibutyl adipate, and from about 0 wt% to about 50 wt% of isopropyl myristate.

4. The composition as defined in claim 1, wherein said pharmacologically active agent comprises a

dermally effective amount of a dermatological agent.

5. A composition as defined in claim 4, wherein said dermatological agent has a cosmetic effect.

6. A composition as defined in claim 4, wherein said dermatological agent is therapeutic in nature.

7. A composition as defined in claim 1, wherein said pharmacological active agent comprises a systemically active amount of a therapeutic agent.

8. A composition as defined in claim 1, wherein said pharmacological agent is from about 0.001% wt to about 80% wt of total composition.

9. A composition as defined in claim 4, wherein the drug affecting the skin is tretinoin, halobetasol propionate, or 11-cis, 13-cis-12-hydroxymethyl retinoic acid, delta lactone.

10. A composition as defined in claim 4, wherein the drug affecting the skin is an α or β hydroxycarboxylic acid or related ketocarboxylic acid or ester, lactone or salt form thereof.

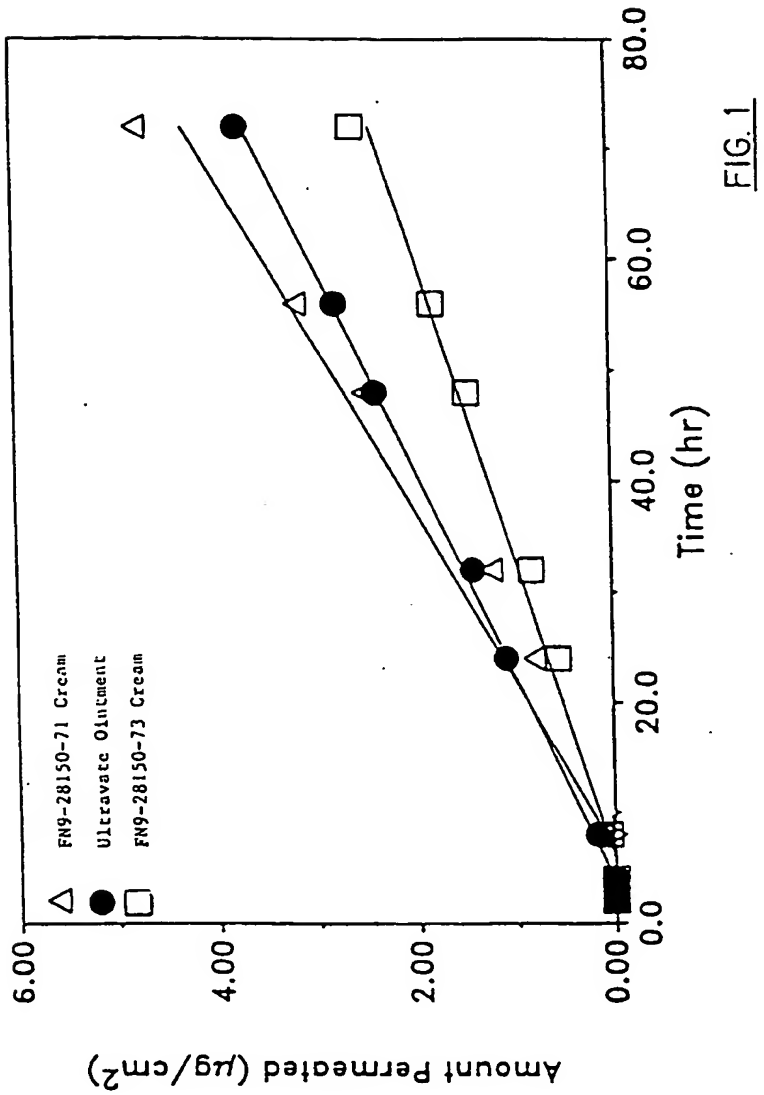
11. A composition as defined in claim 10 wherein the α-hydroxycarboxylic is lactic acid.

12. A composition as defined in claim 10 wherein the α-hydroxycarboxylic acid salt is ammonium lactate.

13. A composition according to claim 1 wherein the pharmacologically active agent is in the form of suspension, saturated solution or solution having degree of unsaturation not more than 1.5.

14. The use of dibutyl adipate or a mixture of dibutyl adipate and isopropyl myristate or a pharmaceutically acceptable acid addition salt thereof together with a pharmacologically active agent for preparing a topical composition for controlled and enhanced dermal penetration as defined in anyone of claims 1 to 13.

15. A process for preparing a topical composition as defined in anyone of claims 1 to 13 which comprises incorporating the pharmacologically active agent into dibutyl adipate or a mixture of dibutyl adipate and isopropyl myristate or pharmaceutically acceptable acid addition salts thereof and a pharmaceutically acceptable non-toxic topical vehicle.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2.00
0.00
0.0
20.0
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60.0
80.0
Time (hr)
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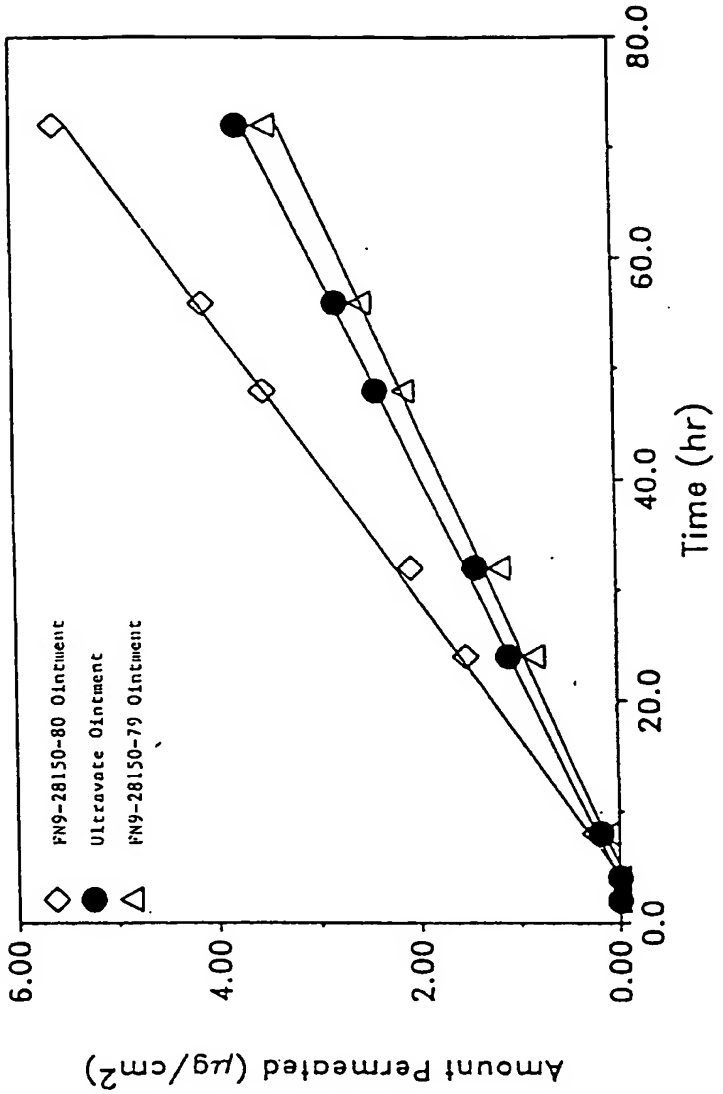
Ultravate Ointment
FN9-28150-73 Cream

FIG. 1


Amount Permeated (μg/cm2)
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4.00
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0.00
0.0
20.0
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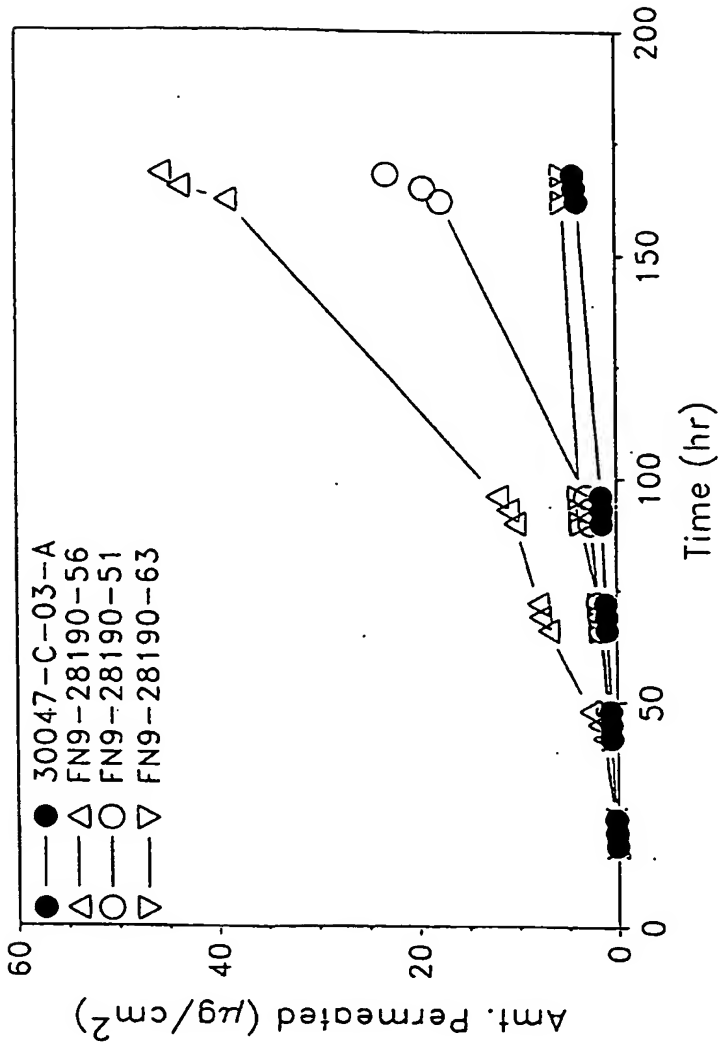
60.0
80.0
Time (hr)
FN9-28150-80 Ointment
Ultravate Ointment
FN9-28150-79 Ointment

FIG.2


Amt. Permeated (μg/cm²)
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20
40
60
0
50
100
150
200
Time (hr)
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FN9-28190-56
FN9-28190-51
FN9-28190-63

FIG.3

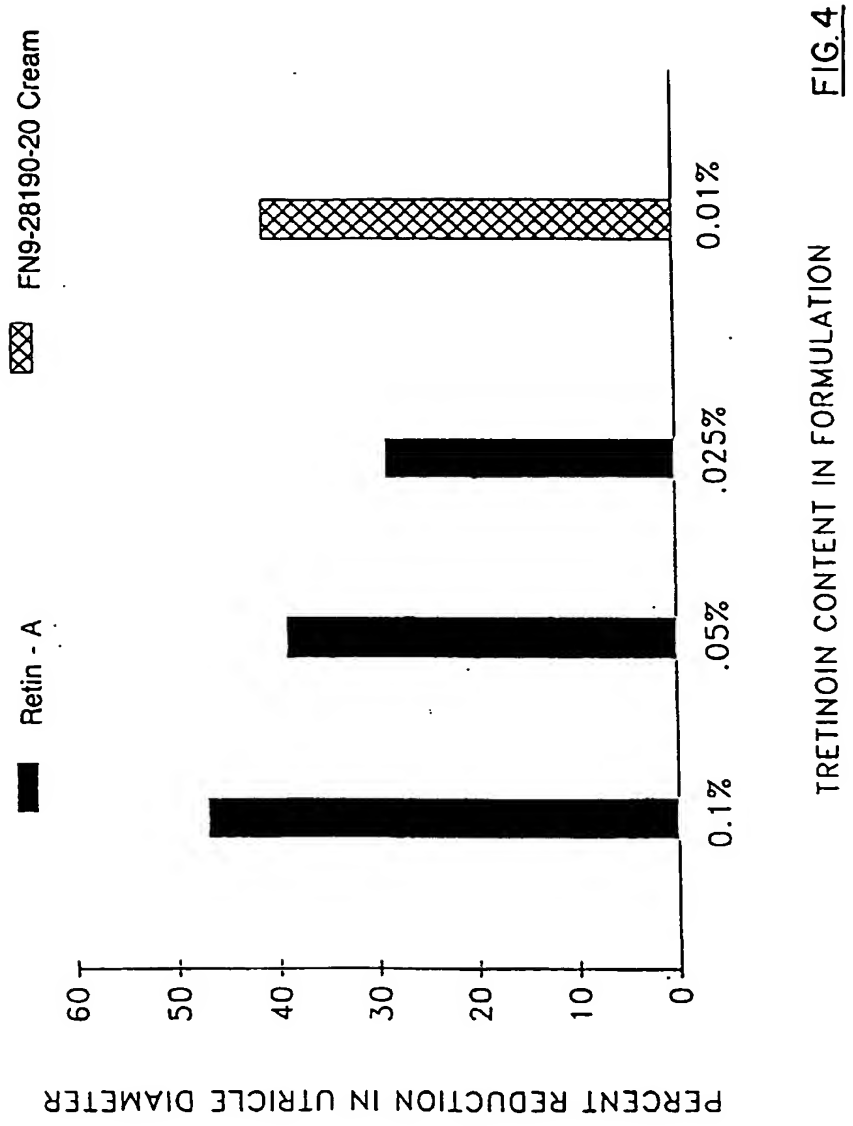
FN9-28190-20 Cream
Retin - A
0.1%
.05%
.025%
0.01%
TRETINOIN CONTENT IN FORMULATION
PERCENT REDUCTION IN UTRICLE DIAMETER
0
10
20
30
40
50
60

FIG.4

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 10 8286

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	BRITISH JOURNAL OF DERMATOLOGY vol. 118, no. 4, April 1988, LONDON pages 523 - 530; WATSON W.S. ET AL: 'THE EFFECT OF THE VEHICLE FORMULATION ON THE STRATUM CORNEUM PENETRATION CHARACTERISTICS OF CLOBETASOL 17-PROPIONATE IN VIVO' * the whole document *	1,2,4-8, 14,15	A61K47/14
X Y	LU-A-84 059 (GLAXO GROUP LTD) * page 1, line 1 - line 3 * * page 3, line 20 - line 27 * * page 7; example 2 * * claims 4-6 *	1-8,13, 15 9-12	
Y	EP-A-0 423 929 (KABUSHIKI KAISHS HAYASHIBARA SEIBUTSU KAGAKU KENKYUJO) * page 10; example 2 * * claims 1,2,3 *	10-12	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
Y	WO-A-8 503 434 (NEUTROGENA CORPORATION) * page 12; example 10 * * claim 1 *	9	A61K
A	WO-A-8 907 951 (RIKER LABORATORIES INC)		

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	27 JULY 1992	BOULOIS D.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,640	12/15/2003	Bruno de Lignieres	029488-0111	9061

22428 7590 05/29/2008

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	**PAPER NUMBER**
1617	
MAIL DATE	**DELIVERY MODE**
05/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,640	LIGNIERES ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 2/21/2008. The terminal disclaimer filed on 2/21/2008 disclaiming the terminal part of the term of any patent granted on U.S. Patent Application 10/734,640 which would extend beyond the full statutory term, as shortened by any terminal disclaimer, of any patent granted on U.S. Patent Application 10/734,638 has been reviewed and accepted. Claim 5 is cancelled. Claims 1-4, 6-14 are pending and are being examined on the merits herein.

Response to Remarks

Applicants' arguments regarding the rejection of claims 1-3, 6-8, 10, 11-14 under 35 U.S.C. 103(a) as being unpatentable over Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) and rejection of claims 1-3, 6-8, 10, 11-14 under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) and rejection of claims 1-3, 6-8, 10,11-14 under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) and rejection of claim 9 under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498,

1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Kochinke et al. (U.S. 5,613,958) and rejection of claim 4 under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Malet et al (Cancer Research, 48, 7193-7199, 1988) have been fully considered and found not persuasive. The rejections are maintained and are given below for Applicants' convenience. The action is made Final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 6-8, 10, 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284)

in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Jarvis teach studies have been performed to determine if 4-hydroxy tamoxifen, a very active metabolite of tamoxifen that has an affinity for the estrogen receptor 100 times greater than that of tamoxifen, can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease. The reference further teaches the results from those studies that 4-hydroxy tamoxifen when topically applied in alcoholic solution over the human breast is absorbed through the skin and is retained. The reference teaches that tamoxifen has been proposed for the treatment of benign breast disease (one of the symptoms being breast pain (mastodynia or mastalgia) but due to drawback of its use in premenopausal women leading to an increase in gonadotropin secretion studies were performed with 4-hydroxy tamoxifen (p 281, col. 1, col. 2, Antiestrogens).

The reference does not teach the amount of 4-hydroxy tamoxifen in the percutaneous administration.

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design).

Jarvis and Pujol et al. do not teach mastalgia to be cyclical.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer 4-hydroxy tamoxifen at a dose of at least 1.5 mg/day or the dosages claimed in the instant invention. One of ordinary skill in the art would have been motivated to administer such claimed amounts of 4-hydroxy tamoxifen in the treatment of mastalgia because of expectation of success as Pujol et al. clearly teaches percutaneous administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia. One of ordinary skill in the art would have been motivated to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia because of the teachings of Fentiman and Jarvis. Jarvis teach the use of 4-hydroxy tamoxifen in benign breast disease (mastalgia, which includes both cyclical and non-cyclical) and the advantages

of using 4-hydroxy tamoxifen over tamoxifen and Fentiman teaches the use of tamoxifen in the treatment of both cyclical and non-cyclical breast pain. It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen for tamoxifen in the treatment of cyclical breast pain as Jarvis teaches the drawbacks of using tamoxifen and the advantages of 4-OH tamoxifen and it is well known in the art that 4-OH tamoxifen is an active metabolite of tamoxifen.

Claims 1-3, 6-8, 10, 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Jarvis et al. teach studies have been performed to determine if 4-hydroxy tamoxifen, a very active metabolite of tamoxifen that has an affinity for the estrogen receptor 100 times greater than that of tamoxifen, can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease. The reference further teaches the results from those studies that 4-hydroxy tamoxifen when topically applied in alcoholic solution over the human breast is absorbed through the skin and is retained. The reference teaches that tamoxifen has been proposed for the treatment of benign breast disease (one of the symptoms being breast pain (mastodynia or mastalgia) but due to drawback of its use in premenopausal women leading to an increase in gonadotropin secretion studies were performed with 4-hydroxy tamoxifen (p 129, 130, Therapeutic Alternatives, Antiestrogens).

The reference does not teach the amount of 4-hydroxy tamoxifen in the percutaneous administration.

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design).

Jarvis and Pujol et al. do not teach mastalgia to be cyclical.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer 4-hydroxy tamoxifen at a dose of at least 1.5 mg/day or the dosages claimed in the instant invention. One of ordinary skill in the art would have been motivated to administer such claimed amounts of 4-hydroxy tamoxifen in the treatment of mastalgia because of expectation of success as Pujol et al. clearly teaches percutaneous administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*,

406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia. One of ordinary skill in the art would have been motivated to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia because of the teachings of Fentiman and Jarvis. Jarvis teach the use of 4-hydroxy tamoxifen in benign breast disease (mastalgia, which includes both cyclical and non-cyclical) and the advantages of using 4-hydroxy tamoxifen over tamoxifen and Fentiman teaches the use of tamoxifen in the treatment of both cyclical and non-cyclical breast pain. It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen for tamoxifen in the treatment of cyclical breast pain as Jarvis teaches the drawbacks of using tamoxifen and the advantages of 4-OH tamoxifen and it is well known in the art that 4-OH tamoxifen is an active metabolite of tamoxifen.

Claims 1-3, 6-8, 10,11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design). The reference further teaches that 4-hydroxy tamoxifen is an active metabolite of tamoxifen (p 497, col. 1, line 18). Pujol et

al. do not explicitly teach 4-hydroxy tamoxifen to be a racemic mixture but it is obvious that the compound has both the cis and trans isomers.

The reference does not teach 4-hydroxy tamoxifen in the treatment of mastalgia.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use 4-hydroxy tamoxifen in the treatment of mastalgia. The motivation to do so is provided by Pujol et al. The reference teaches that 4-OH-tamoxifen is an active metabolite of tamoxifen and has 100-1000 fold stronger affinity to estrogen receptors compared to tamoxifen and the reference further teaches 4-OH-tamoxifen to be one of the most potent anti-estrogens and the compound penetrates through the skin. The reference also teaches that 4-OH-tamoxifen gel administration is associated with low systemic effects yet induces moderate breast tissue concentration.

Fentiman et al. and Pujol et al. do not teach administration of 0.75mg/breast of 4-OH-tamoxifen or a dose of 1.5 mg/day to patients but Pujol teaches administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients.

The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what

is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Kochinke et al. (U.S. 5,613,958).

The teachings of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) have been discussed in the 103(a) rejection set forth above.

Pujol et al. and Fentiman et al. do not teach the hydroalcoholic gel comprising ethanol, isopropyl myristate and hydroxypropyl cellulose.

Kochinke et al. teaches a transdermal drug delivery system comprising a drug, plasticizer-type enhancer such as isopropyl myristate, a solvent-type enhancer such as ethanol and a gelling agent such as hydroxypropyl cellulose (col. 9, lines 23-25, 47-59, col. 11, lines 6-25).

It would have been obvious to one of ordinary skill in the art to use a combination of isopropyl myristate, ethanol, and hydroxypropyl cellulose as a hydroalcoholic gel solution in the percutaneous delivery of 4-OH tamoxifen. The motivation to do so is

provided by Kochinke et al. The reference teaches that solvent-type enhancer such as ethanol provide higher flux rate, plasticizer-type enhancer such as isopropyl myristate is used in combination with a solvent-type enhancer to deliver drugs through stratum corneum at therapeutically effective levels and to eliminate the irritation that occurs when solvent-type enhancers are used alone at high concentrations. In addition the reference teaches that a gelling agent such as hydroxypropylcellulose is added to increase the viscosity and rheological characteristics of the drug and enhancers.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Malet et al (Cancer Research, 48, 7193-7199, 1988).

The teachings of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) have been discussed in the 103(a) rejection set forth above.

Pujol et al. and Fentiman et al. do not teach percutaneous administration of trans 4-hydroxy tamoxifen in the treatment of mastalgia.

Malet teaches percutaneous administration of trans 4-hydroxy tamoxifen to human breast of patients (see Abstract). The reference further teaches that trans-4-hydroxy tamoxifen is a very active metabolite of tamoxifen.

It would have been obvious to one of ordinary skill in the art to use trans 4-hydroxy tamoxifen for the treatment of mastalgia. The motivation to do so is provided by Malet et al. The reference teaches that trans-4-hydroxy tamoxifen is a very active

metabolite of tamoxifen. The reference further teaches that cis-4-hydroxy tamoxifen exerts a potent estrogenic agonistic effect and a percutaneous administration of trans 4-hydroxy tamoxifen could produce a strong antiestrogenic effect at the molecular level.

Response to Arguments

Applicants' arguments regarding the rejections have been fully considered and found not to be persuasive. Applicants' argue that tamoxifen is not a prodrug of 4-OH tamoxifen and 4-OH tamoxifen is one of the three primary metabolites and not even a major metabolite. In response, it is not relevant that 4-OH tamoxifen is not a major metabolite but it is well known in the art that it is one of three primary metabolites. Applicants' further argue that someone skilled in the art would not expect 4-OHT to be biologically equivalent to tamoxifen based on the estrogen receptor binding affinity. It is known in the art that structurally related compounds might or might not have the same or equivalent biological activity because a small difference in the substitution can lead to different biological activities. Yet it would have been obvious to one of ordinary skill in the art at the time of the invention to administer 4-OHT in a method of treatment of mastalgia because 4-OHT is known to be an active metabolite and one of the primary metabolites of tamoxifen and further Jarvis's studies clearly suggests that the administration of 4-OH tamoxifen in the treatment of benign breast disease for tamoxifen to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease. Applicants' argue that one of skilled in the art would not have administered 4-OHT for tamoxifen in the treatment of mastalgia because commercially available Z-isomer of tamoxifen yields only Z-isomer of 4-OHT that has only anti-

estrogenic activity. This is not persuasive because, the relative anti-estrogenic activity will depend on the amount of isomers present in the mixture and may not result in the estrogenic activity alone. In addition Jarvis et al. (U.S. 4,919,937) clearly teaches the benefits of 4-OH tamoxifen in benign cancer conditions and Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) teach mastodynia or mastalgia is associated with benign breast disease. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to have adminstered 4-OHT in a method of treatment of mastalgia. Applicants' argue that "different tamoxifen metabolites have different activities, tamoxifen has a number of biological activities and a number of biological active metabolites a priori, and predicting which specific activity and metabolite of tamoxifen might be useful for the treatment of breast condition is not an undertaking that can be carried out with any reasonable level of uncertainity". In response this is not persuasive because there is prior art that teaches and suggests the administration of 4-OH tamoxifen in a method of treatment of benign breast diseases (Jarvis et al. (U.S. 4,919,937), Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284), Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132). As stated above mastalgia or mastodynia is associated with benign breast disease. In addition there are only three primary metabolites of tamoxifen and 4-OH tamoxifen being an active metabolite with an affinity for the estrogen receptor 100 times greater than that of tamoxifen, the level of uncertainity seems to be very low. It would have been clearly obvious from the prior literature to one of ordinary skill in the art that 4-OH

tamoxifen would be useful in a method of treatment of mastalgia. Also, as pointed out by the Applicants' that different metabolites have different biological activities one of skilled in the art would have been motivated to find out which metabolite of tamoxifen is responsible for the biological activity of tamoxifen. Applicants argue that other tamoxifen metabolites such as Droloxifene or another estrogen receptor modulator such as raloxifene has high level of unpredictability and hence the skilled artisian could not have reasonably predicted from the known estrogen binding activity of 4-OHT that 4-OHT could be used to treat mastalgia. This is not persuasive because if a metabolite of tamoxifen or an estrogen receptor modulator is less effective than tamoxifen does not mean that other metabolites cannot be used or will not be useful in a method of treatment of a disorder. In addition, one of ordinary skill in the art would have been motivated to test the other two primary metabolites after learning that droloxifene is found to be less effective than tamoxifen. Applicants' argue that 4-OHT is not the only active metabolite of tamoxifen for pharmacological activity and was not necessarily the most promising or viable choice for further study. This is not persuasive because it is irrelevant whether 4-OHT is not the only active metabolite of tamoxifen. The prior art teaches and suggests the administration of 4-OH tamoxifen in a method of treatment of benign breast diseases (Jarvis et al. (U.S. 4,919,937), Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284), Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132). Hence the prior art clearly suggests that 4-OHT is a promising choice in a method of treatment of benign breast diseases. Applicants' argue

that the prior art Pujol studies comes from post-menopausal breast cancer patients and the present invention relates to the treatment of mastalgia, a condition that arises in pre-menopausal patients. The arguments are not persuasive because, the primary reference Jarvis teach teaches and suggests the administration of 4-OH tamoxifen in a method of treatment of benign breast diseases The reference teaches that tamoxifen has been proposed for the treatment of benign breast disease (one of the symptoms being breast pain (mastodynia or mastalgia)). The secondary reference Pujol has been used to show the amount of 4-OHT that can be safely applied to breasts. It would have been obvious to one of ordinary skill in the art at the time of the invention that 4-OHT can be used in a method of treatment of benign breast diseases such as mastaglia from Jarvis's teachings. If the same drug as claimed is taught to be useful in a method of treatment of benign breast disease such as masgtalgia then the treatment applies to the same set of population. Applicants' argue that Pujol reference does not suggest that percutaneous 4-OHT can be successfully used in place of oral tamoxifen to breast cancer, let alone to treat mastalgia. In response, as stated earlier, Jarvis teach that 4-OHT can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease. It would have been obvious to one of ordinary skill in the art at the time of the invention that 4-OHT can be used percutaneously in the treatment of benign breast disease. Applicants' argue that Jarvis's references are entirely speculative and not based on supporting clinical data. In response, Jarvis's teachings are used in the obviousness rejections. It would have been obvious from the teachings of Jarvis that benign breast diseases can be treated with the administration of

4-OHT. The studies clearly suggest and motivate a person of ordinary skill in the art to use 4-OHT in a method of treatment of benign breast disease, one of the symptoms being breast pain or mastalgia.

Conclusion

No claims are allowed.

The rejections are maintained and are given in the Office Action for Applicants' convenience. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The

fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617